REMARKS

Claims 1-19, 44, 46, and 70-96 are currently pending in the above-identified application and remain for consideration. Claims 20-43, 45, and 47-69 have been cancelled as having been withdrawn to a Restriction Requirement that has been made final. Claims 70-96 have been added by this amendment.

Claims 7 and 8 were allowed.

Claim 12 was objected to as being dependent on a rejected base claim, but was considered to be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The specification was objected to for the recitation of improperly demarcated trademarks.

The specification was further objected to because of the failure to include sequence identifiers for a number of nucleotide and/or amino acid sequences.

The specification was also objected to for certain informalities.

Claims 1, 9-11, 13-18, 44, and 46 were rejected under the first paragraph of 35 U.S.C. § 112 for failure to comply with the written description requirement.

Claims 1-6, 9-11, 13-19, 44, and 46 were rejected under the first paragraph of 35 U.S.C. § 112 for failure to comply with the enablement requirement.

Claims 13, 15, and 19 were rejected under 35 U.S.C. § 102(b) as anticipated by K. Fatyol et al., "Molecular Characterization of a Stably Transformed *Bombyx mori* Cell Line: Identification of Alternative Transcriptional Initiation Sites of the A3 Cytoplasmic Actin Gene," Mol. Gen. Genet. 260: 1-8 (1998) ("Fatyol et al. (1998)) as evidenced by Q. Huang et al., "Cloning and Characterization of an Inhibitor of Apoptosis Protein (IAP) from *Bombyx mori*," Biochim. Biophys. Acta 1499: 201-208 (2001) ("Huang et al. (2001)") and the USPTO Search Reports "us-10-041-859-2.rge" and "us-10-041-859-1.rge" (collectively "the Alignments").

Reexamination of the application as amended, reconsideration of the rejections and objections, and allowance of the claims not already considered allowable are respectfully requested.

The period for response has been extended until July 16, 2005 by the simultaneous filing of a two-month Request for Extension of Time under 37 C.F.R. § 1.136(a). The United States Patent and Trademark Office is respectfully requested to charge the required fee of $225.00 (small entity) to Deposit Account No. 502-235. Accordingly, this response is being filed in a timely manner.

I. AMENDMENTS TO THE APPLICATION

Entry of the amendments to the application is respectfully requested. As detailed below, the amendments introduce no new matter.

The specification is amended to clearly identify trademarks where appropriate, and to correct certain typographical errors, such as "nemotode" for nematode and the names of certain groups of viruses at page 20, lines 26-27 of the specification. No new matter is introduced by these corrections.

The recitation of the domains of BmIAP is supported in the specification at page 32, lines 19-25. These domains are clearly part of novel recombinant proteins of the invention and recitation of them in claims does not introduce new matter.

Similarly, the recitation in claim 1 and other independent claims of inhibition of a caspase is supported in the specification at page 35, lines 24-25.

This response is being filed in accordance with recently revised 37 C.F.R. § 1.121, as set forth in 68 F.R. 38611 (June 30, 2003). If the amendment is considered to be not in compliance with recently revised 37 C.F.R. § 1.121, the Examiner is respectfully requested to contact the undersigned at his earliest possible convenience.

Accordingly, entry of these amendments is respectfully requested.

II. THE OBJECTIONS TO THE SPECIFICATION

A. The Objection to the Specification for Use of Improperly Demarcated Trademarks

The specification was objected to for the use of improperly demarcated trademarks. In response, all trademarks used in the specification have been capitalized and

are used together with a symbol indicating their status as trademarks. Accordingly, the Examiner is respectfully requested to withdraw this objection.

B. The Objection to the Specification for Failure to Recite Sequence Identification Numbers

The specification was objected to for failure to recite sequence identification numbers for sequences allegedly recited at the following locations within the specification: page 8, line 9; page 8, line 13; page 8, line 13; page 29, lines 3 and 4; page 31, lines 20-54 (the "coding region nucleotide sequence"); page 34, line 12; page 35, line 2; page 35, line 4; page 35, line 18; and 35, line 26.

With the single exception of page 31, lines 20-54 (the "coding region nucleotide sequence"), this objection is respectfully traversed. All of the other locations within the specification recited in the Office Action do not actually recite a specific sequence by providing that sequence in terms of an amino acid sequence or a nucleotide sequence that is given in full in the specification. These references are not to a sequence that is actually contained in the specification as required by 37 C.F.R. § 1.821 (c) and (d). With the exception of the sequence recited at page 31, lines 20-54 (the "coding region nucleotide sequence"), none of the other references are to sequences that are actually contained in the specification, in the sense of the full sequence being actually presented at some point in the specification or figures. Rather, the reference is to a publication or another source. There is no basis for applying the sequence listing rules to sequences that are not actually set forth in the specification.

For the sequence recited at page 31, lines 20-54 (the "coding region nucleotide sequence"), a SEQ ID NO (SEQ ID NO:1) is provided.

Accordingly, the Examiner is respectfully requested to withdraw this objection to the specification as amended.

C. The Objection to Other Informalities in the Specification

Certain other informalities in the specification were objected to. Specifically, at page 28, line 28, "1999" was mistyped as "19999". This typographical error has been corrected. Also, at page 16, lines 14-15, the specification originally read "[i]f a

polynucleotide sequence has the requisite sequence identity to SEQ ID NO:2 . . ." However, SEQ ID NO:2 is a polypeptide sequence. This misreference has also been corrected.

Therefore, the Examiner is respectfully requested to withdraw these objections to the specification as amended.

III. THE REJECTIONS UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112

A. The Rejections of Claims 1, 9-11, 13-18, 44, and 46 for Alleged Failure of Compliance with the Written Description Requirement

Claims 1, 9-11, 13-18, 44, and 46 were rejected under the first paragraph of 35 U.S.C. § 112, allegedly for lack of compliance with the written description requirement. To the extent that the amendments to the claims have not obviated this rejection, it is respectfully traversed.

As amended, these claims now recite structural features present in the proteins encoded by the nucleic acid molecules, including at least one of: (1) a domain having the function of the BIR1 domain and (2) a domain having the function of the RING domain. The claims also recite that the polypeptide encoded by the nucleic acid segment inhibits the activity of a caspase. These structural features of the encoded polypeptides, which are related to the activity of the polypeptides in inhibiting a caspase, are sufficient to meet the requirements for written description of the first paragraph of 35 U.S.C. § 112.

The basic test under the written description requirement of 35 U.S.C. § 112 is well established. All that is required to satisfy the written description requirement of the first paragraph of 35 U.S.C. § 112 is that the patent specification describes the claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed subject matter, to ensure, e.g., that the invention had possession of the claimed subject matter as of the desired priority date. Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997). In the context of nucleic acids, the recitation of structure for the claimed subject matter need not be great in order to satisfy the written description requirement. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of a genus or of a recitation of structural features common to the

members of the genus, which features constitute a substantial portion of the genus." Regents of the University of California, 43 U.S.P.Q. 2d at 1406. Moreover, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in the application by "other appropriate language." Id.

This basic standard for compliance with the written description requirement under the first paragraph of 35 U.S.C. § 112 is satisfied by recitation of the required degree of identity in the claims, in conjunction with the structural and functional features of the polypeptide sequences encoded by the nucleic acid sequences. Identity of a nucleic acid sequence is a strict standard; either two bases in a sequence are identical, when the sequences are properly aligned, or they are not identical. Therefore, the percentage of identity recited in these claims provides sufficient relevant identifying characteristics to meet this standard.

The "Guidelines for Examination of Patent Examinations Under the 35 USC § 112 para. 1 'Written Description' Requirement," 66 Fed. Reg. 1099 (January 5, 2001) issued by the United States Patent and Trademark Office, state that the policy goals of the written description requirement are to: (i) clearly convey to the public what was invented; (ii) put the public in possession of what the applicant claims as the invention; and (iii) prevent an applicant from claiming subject matter that was not described in the specification as filed. These policy requirements are met by the amended claims.

Moreover, possession of the claimed invention can be shown by any of: (1) actual reduction to practice; (2) a "clear depiction" of the invention in detailed drawings; or (3) a description of sufficient relevant identifying characteristics. These requirements are met. There is actual reduction to practice in terms of the recitation of SEQ ID NO:1 and the protein encoded by this sequence, SEQ ID NO:2. There is also actual reduction to practice in terms of the identification of the domains involved in caspase inhibition, such as the BIR1 domain, the BIR2 domain, and the RING domain (specification at page 32, lines 19-33). This is sufficient to meet the requirements of the first paragraph of 35 U.S.C. § 112.

It is not the purpose or rationale of the written description requirement to define the function of claimed nucleic acid sequences. Once sufficient identifying characteristics are provided to enable one of ordinary skill in the art to conclude that the inventors had possession of the invention, the written description requirement has been

satisfied. The nucleic acid sequences recited meet the requirements of 35 U.S.C. § 101 for utility, and the written description requirement cannot be used to contravene that finding.

The specification is sufficient to describe the invention "so that one skilled in the art can recognize what is claimed." Enzo Biochem, Inc. v. Gen-Probe, Inc., 62 U.S.P.Q. 2d 1289, 1293-94 (Fed. Cir. 2002) ("Enzo I"). That standard is clearly met here. Moreover, it is well-established that an applicant need not disclose every species encompassed by a claim. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976).

The comments made in the Office Action, when considered with respect to the amended claims, do not give rise to a rejection for lack of compliance with the written description requirement under the first paragraph of 35 U.S.C. § 112. Specifically, the class of nucleic acids recited in the claims does not "include members that vary markedly in function" because the members do not, in fact, "encode polypeptides that vary in both structure and function" in light of the recitation of a defined activity of these polypeptides and the presence in these polypeptides of well-defined domains.

Similarly, Applicants now have "described identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed." Moreover, as applied to the amended claims, the members of the class of nucleic acid residues recited in the claims are "necessarily functionally related" to the nucleic acid molecule of SEQ ID NO:1. This functional relation is provided by the recitation of the domain and by the function of the protein encoded by the nucleic acid molecule in inhibiting a caspase. This is also the "common functional feature" referred to.

Specifically, this amendment meets the suggestion made at page 7, lines 8-16 of the Office Action. The amendments to the claims mean that the claims are directed to "a polypeptide having or retaining a disclosed, particularly identifying functional property of the polypeptide of SEQ ID NO: 2 that correlates with a particularly identifying structural feature common among the members of the genus of polypeptides encoded by the nucleic acid molecule of SEQ ID NO: 1 and the other nucleic acids also encompassed by the claims."

Accordingly, this rejection is respectfully traversed as applied to the amended claims. The Examiner is therefore respectfully requested to withdraw the rejection.

B. The Rejection of Claims 1-6, 9-11, 13-19, 44, and 46 for Alleged Failure of Compliance with the Enablement Requirement

Claims 1-6, 9-11, 13-19, 44, and 46 were rejected under the first paragraph of 35 U.S.C. § 112, allegedly for lack of compliance with the enablement requirement.

Specifically, it was stated that the specification was enabling for making and using a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO:1 and encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an expression cassette comprising the polynucleotide sequence of the nucleic acid molecule, an isolated transformed cell comprising the nucleic acid molecule, an array comprising the nucleic acid molecule, and a method for producing a recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 comprising expressing the nucleic acid molecule. However, according to the Office Action, the specification did not reasonably provide enablement for making and using a nucleic acid molecule comprising a sequence that is not identical to SEQ ID NO: 2 or encoding a polypeptide comprising an amino acid sequence that is not identical to SEQ ID NO: 2, or an expression cassette comprising the polynucleotide sequence of the nucleic acid molecule, or a transformed cell comprising the nucleic acid molecule, or an array comprising the nucleic acid molecule, or a method for producing a recombinant polypeptide comprising expressing the nucleic acid molecule.

As applied to the amended claims, this rejection is respectfully traversed.

It is established law with respect to enablement that the specification must be taken as being in compliance with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective role of the statements contained in the specification which must be relied upon for enabling support. In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971). There has in fact been no suggestion that it would constitute undue experimentation to make or use any of the nucleotides within the scope of the claims. Methods for the preparation of nucleotide sequences, including PCR amplification and solid-phase polynucleotide synthesis, to name several techniques, are well understood in the art and there use to create any sequence within the scope of the claims would not constitute undue experimentation. Also, it is relatively simple for one of ordinary skill in the art to use appropriate software programs such as BLAST to provide a nucleotide-by-nucleotide comparison of sequences to determine whether they meet any specified level of identity, such as 95% sequence identity. This also

does not constitute undue experimentation. Furthermore, it is well within the skill of the art to determine the polypeptide sequence encoded by any particular polynucleotide, using the standard triplet genetic code and identifying open reading frames in one of the three possible reading frames by the presence of an initiatory AUG (methionine) codon in that reading frame. Additionally, it is also well within the skill of the art to produce polypeptides of completely defined sequence encoded by a nucleotide segment, such as by recombinant DNA technology that places the nucleotide segment into an environment suitable for its expression. Finally, the assays required for determining inhibition of caspase activity are well within the skill of the art. Caspases are proteases, and protease activity can be monitored by use of suitable substrates, such as chromogenic substrates, under well-defined reaction conditions.

Moreover, properly reasoned and supported statements explaining any failure to comply with the enablement requirements of 35 U.S.C. § 112 are a requirement to properly support such a rejection. The absence of such properly reasoned and supported statements compels withdrawal of this rejection. In re Wright, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993). The Office Action merely states: "Without a clear disclosure of the sequences encompassed by the claims one of skill in the art would not know how to make or use the claimed invention without performing an undue amount of additional experimentation to first identify the sequences having the desired function." That statement does not provide "properly reasoned and supported statements" as to why enablement is not present. The question, from the standpoint of compliance with the enablement requirement of the first paragraph of 35 U.S.C. § 112, is whether the specification enables one of ordinary skill in the art to prepare and use the required nucleotide sequences, expression cassettes, transformed cells, or arrays. The answer, in view of the specification and examples, to this question is undoubtedly affirmative.

The specification need not recite details of the claimed invention where one of ordinary skill in the art would consider these details obvious or well known in the art. In re Skirvan, 427 F.2d 801, 166 U.S.P.Q. 85 (C.C.P.A. 1970). The quantity of detail permitted to be omitted can be substantial when the state of the art is such that the detail could be readily supplied by one of ordinary skill in the art. This is true even if no working examples are furnished. In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (immunochemistry).

Even should considerable experimentation be required, this does not constitute "undue experimentation" if the experimentation required is routine and the worker is given sufficient guidance. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). Thus, the amount of experimentation that *might* be required does not give rise to a conclusion of lack of enablement. Moreover, complete reproducibility is not required to find enablement. Johns Hopkins University v. CellPro, Inc., 47 U.S.P.Q. 2d 1705 (Fed. Cir. 1998). In fact, under the holding of Johns Hopkins University, the fact that some attempts at reproducing the claimed invention fail does not lead to a conclusion of undue experimentation. In Johns Hopkins University, the invention concerned monoclonal antibodies, and attempts to reproduce the claimed invention did not uniformly result in success. The Federal Circuit held that this did not constitute undue experimentation, because a certain amount of experimentation was inherent in the Kohler-Milstein process for producing monoclonal antibodies, and a certain degree of irreproducibility was expected. Id. As explained above, even though a considerable amount of experimentation may be required, the experimentation can be broken down, step by step, and is routine. Moreover, the results of each step can be used in a routine manner to plan the next step of experimentation.

The degree of unpredictability must be considered within the context of the invention and the knowledge of those skilled in the art. Even broad claims can be enabled if the subject matter of the claims is such that the unpredictability of what is actually claimed is minimized. See In re Vaeck, 20 U.S.P.Q. 2d 1438, 1444-45 (Fed. Cir. 1991) (claims directed to expression of chimeric genes in specific genera of cyanobacteria allowable even though claims were not limited to expression of genes encoding particular Bacillus proteins in view of extensive understanding in the prior art of toxicity of Bacillus proteins). In view of the scope of the claims and the requirements for the conservation of domains involved in inhibition of caspase activity, the subject matter of the claims cannot be considered to be unpredictable. This is another strong argument for enablement of the claimed invention.

All that is required to provide enablement is that any mode of making and using the invention be recited in the specification. Engel Industries, Inc. v. Lockformer

Corp., 946 F.2d 1528, 20 U.S.P.Q. 2d 1300 (Fed. Cir. 1991). This test is clearly met here by the specification in view of what is known in the art.

Moreover, there is no requirement that all compositions within the scope of the claimed methods provide the same degree of efficacy or activity. In re Gardner, 177 U.S.P.Q. 396 (C.C.P.A. 1973); In re Fouche, 169 U.S.P.Q. 429 (C.C.P.A. 1971). The fact that some of these nucleotide sequences may, for example, encode proteins that have a greater inhibitory effect on apoptosis, through inhibition of caspases, than others does not mean that undue experimentation exists.

As is frequently the case in enablement questions, a review of the factors set forth by the Federal Circuit in In re Wands, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), is useful. The Wands factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented: (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Id.

A review of these factors indicates that enablement is present. The conclusion is that a rejection under the first paragraph of 35 U.S.C. § 112 should be withdrawn.

The quantity of experimentation required is not excessive in view of the subject matter. As indicated above, methods for performing all of the steps needed to determine the activity of the claimed sequences against apoptosis and their inhibition of a caspase are well understood in the art. When these methods are combined with the teachings of the specification, there is only a moderate degree of experimentation to be carried out by one of ordinary skill in the art. What experimentation is required is routine in view of the well-understood nature of the methods and in view of the ability of one of ordinary skill in the art to interpret the results. As emphasized above, one skilled in the art can readily prepare the nucleotide sequences, can use appropriate software programs such as BLAST to provide a nucleotide-by-nucleotide comparison of sequences to determine whether they meet any specified level of identity, such as 95% sequence identity, can determine the polypeptide sequence encoded by any particular polynucleotide, can produce polypeptides of completely defined sequence encoded by a nucleotide segment, such as by recombinant DNA technology

that places the nucleotide segment into an environment suitable for its expression, and can perform the assays required for determining inhibition of caspase activity.

The nature of the invention is such that undue experimentation is not present, when the scope of the claimed invention is taken into account. The claimed invention, from the standpoint of enablement, is of a relatively restricted scope as to what must be shown to constitute enablement. The activities of these nucleic acid sequences in encoding apoptosis-inhibiting proteins are not in question. These are not claims for which a degree of extrapolation is required such that the extrapolation would lead to a conclusion of undue experimentation based on the burden placed on one of ordinary skill in the art to achieve enablement within the scope of the claimed invention. Compare In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (enablement found even though no working examples present) with In re Fisher, 427 F.2d 833, 166 U.S.P.Q. 18 (C.C.P.A. 1970) (no enablement for claims to an ACTH preparation having a potency of at least 1 international unit/mg, with no upper limit, when specification disclosed preparation of ACTH of potency between 1.11 and 2.30 international units/mg). Here, the scope of the protection sought is relatively circumscribed and the degree of experimentation required is minimal.

The state of the prior art does not suggest an exceptional degree of unpredictability with respect to the structure or function of these nucleotide sequences, or with respect to the resulting inhibition of caspase activity, leading to an inhibition of apoptosis. As recited above, it is extremely easy for one of ordinary skill in the art to determine sequences that meet the criterion of a specified degree of identity to SEQ ID NO:1 and then to synthesize or replicate such sequences, as well as to perform the other steps required to determine the activity of polypeptides encoded by such sequences.

The relative skill of those in the art is high. This invention is directed to biochemists, microbiologists, and cell biologists, typically with a Ph.D. or other advanced degree in the relevant discipline.

The predictability or unpredictability of the art was discussed above. As indicated, the degree of unpredictability in the structure and function of these sequences is reduced by the availability of well-understood algorithms for determining the degree of identity between two nucleotide sequences and by the availability of well-understood tools for synthesis or replication of these sequences. The degree of unpredictability in the

structure and function of these sequences is reduced by the recitation of conserved domains in the claims.

In fact, the Federal Circuit itself, in Wands, found that enablement existed and that undue experimentation was not present. It held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d at 737, 8 U.S.P.Q. 2d at 1404. Wands involved monoclonal antibodies produced by hybridomas. The monoclonal antibodies had to have a certain degree of affinity toward their corresponding antigen. Of 143 hybridomas produced, only 9 were screened further, and of those 9, only four were found to fall within the scope of the claimed invention. This was sufficient to find enablement in the technology under consideration.

The fact that some sequences within the scope of the claims may not have the desired function of encoding a polypeptide that inhibits a caspase, thus inhibiting apoptosis, does not give rise to a finding of undue experimentation and thus lack of enablement under the first paragraph of 35 U.S.C. § 112. Atlas Powder Co. v. E.I DuPont de Nemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984).

As long as the specification discloses at least one method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claimed invention, the enablement requirement of the first paragraph of 35 U.S.C. § 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). That test is met here in view of the teachings of the specification and the knowledge of those in the art.

The situation here is analogous to that in Wands. The claims are of such a scope that one of ordinary skill in the art could use the claimed invention with a reasonable probability of success. That is all that is required for to meet the requirement for enablement under the first paragraph of 35 U.S.C. § 112.

In addressing the comments in the Office Action as applied to the amended claims, the comment at page 9, lines 17-18 that "claims 1, 9-11, 13-18, 44, and 46 are not limited to nucleic acid molecules encoding a polypeptide having any particular function" is no longer apposite. These nucleic acid molecules do encode a polypeptide having a defined function, that of inhibiting a caspase and thus inhibiting apoptosis.

Similarly, the comment at page 9, lines 20-26 is no longer accurate as applied to the amended claims. This comment reads: "Accordingly, claims 1-6, 9-11, 13-18, 44, and 46 are directed to a genus of nucleic acids that comprise a polynucleotide sequence, which is at least 95% identical to SEQ ID NO: 1, but which either does or does not encode a protein, does or does not encode a protein comprising the amino acid SEQ ID NO: 2, or does or does not encode a protein capable of inhibiting the incidence of apoptosis or the activity of caspase-9." As amended, these claims are directed to a genus of nucleic acids that does encode a protein and encodes a protein that inhibits apoptosis. The protein does so by inhibiting a caspase, which can be caspase-9.

The first reference cited by the Office Action is J. Skolnick & J.S. Fetrow, "From Genes to Protein Structure and Function: Novel Applications of Computational Approaches in the Genomic Era," Tibtech 18: 34-39 (2000) ("Skolnick & Fetrow (2000)"). The fact cited in Skolnick & Fetrow (2000) that sequence-based approaches to function prediction have "significant limitations" does not create a *prima facie* case of enablement in this instance. The mere possibility or supposition that certain nucleotide sequences within the claims do not encode polypeptides with the desired function cannot defeat enablement. The corollary of this proposition is that it would be necessary to test all sequences within the scope of the claims for enablement to exist, a corollary that flatly contradicts the holding of In re Marzocchi, among other leading cases. Skolnick and Fetrow (2000) itself acknowledges that homology can be used to predict structure. "For proteins whose sequence identity is above ~30%, one can use homology modeling to build the structure." (Skolnick & Fetrow (2000), p. 36, column 2, lines 1-3).

The same argument applies to the second reference cited by the Office Action, J.U. Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247: 1306-1310 (1990) ("Bowie et al. (1990)"). The significance of Bowie et al. (1990) must be minimized because of the advances in the understanding of protein structure and the role that conserved domains play in the tertiary and quaternary structure of proteins that had occurred between 1990 and the filing date of the above-identified patent application. Moreover, Bowie et al. emphasizes that many hydrophobic residues, which are buried in the interior core of the protein, can be substituted with other hydrophobic residues, and also that many hydrophilic residues located on the surface of the

three-dimensional protein structure can be substituted with other hydrophilic residues without altering the three-dimensional structure of the protein. The fact that structure prediction from sequence was "extremely complex" in 1990 cannot be used to reach a conclusion that the claims, as amended, lack enablement. The reasoning is the same as for Skolnick & Fetrow (2002). In the absence of more specific evidence that substantial portions of the subject matter within the scope of the claims is inoperative, there is no *prima facie* case of lack of enablement.

Similarly, the third reference cited in the Office Action, W.H. Burgess et al., "Possible Dissociation of the Heparin-Binding (Acidic Fibroblast) Growth Factor-1 from Its Receptor-Binding Activities by Site-Directed Mutagenesis of a Single Lysine Residue," J. Cell. Biol. 111: 2129-2138 (1990) ("Burgess et al. (1990)"), does not create a *prima facie* case of lack of enablement. The results of Burgess et al. (1990) do not support the general proposition that even a single conservative amino acid substitution can adversely affect the function of the protein. Firstly, the substitution of lysine by glutamic acid cannot really be considered conservative. Lysine and glutamic acid have opposite charges, so, to the extent that the charged residue forms a salt bridge with a moiety of opposite charge to stabilize the protein, the replacement of lysine with glutamic acid cannot be considered conservative.

The same reasoning applies to the findings reported in E. Lazar et al., "Transforming Growth Factor α: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities," Mol. Cell. Biol. 8: 1247-1252 (1988). The replacement of aspartic acid at position 47 with serine or glutamic acid did reduce activity, but did not abolish it; activity remained detectable (Table 1). Moreover, these results related to a system in which modified proteins were expressed in yeast (a heterologous system), and the results of Table 1 suggested that expression was also down together with activity. This makes it far from clear that the results seen were actually due to reduced specific activity of the protein; there may have been some factor influencing expression in this heterologous system. In addition, a replacement of aspartic acid with serine cannot be seen as truly conservative. Serine is a polar amino acid but is uncharged, so, as described above, any ionic interactions such as salt links which the original aspartic acid residue participated in would be lost. This may have an adverse effect on protein structure. Moreover, mere variations in activity do not

create a *prima facie* case of lack of enablement. No particular level of activity is required by the claims.

Similarly, the teachings of L.A. Luque et al., "A Highly Conserved Arginine Is Critical for the Functional Folding of Inhibitor of Apoptosis (IAP) BR Domains," Biochemistry 41: 13663-13671 (2002) ("Luque et al. (2002)") do not give rise to a *prima facie* case of lack of enablement. There is no basis from concluding from the finding that the substitution of a single highly conserved amino acid in the Op-IAP of the baculovirus *Orgyia pseudotsugata* or in the *Drosophila* DIAP1 abolishes the function of the proteins, as defined by their ability to bind apoptosis stimulators, that the proposed range of nucleic acid segments encoding apoptosis inhibitors is not enabled. This conclusion is not based on information that is specific enough to the claimed sequences to enable one of ordinary skill in the art to conclude that there is lack of enablement. There is no teaching in Luque et al. (2002) or any other reference that the particular amino acids in the Op-IAP of the baculovirus *Orgyia pseudotsugata* or in the *Drosophila* DIAP1 that abolish the function of binding to apoptosis stimulators are found in the proteins under consideration. For one thing, the proteins encoded by the nucleic acid segments recited in the claims have not been shown to exert their activity by binding to apoptosis stimulators. In fact, these proteins act by inhibiting the activity of one or more caspases. There is no suggestion or teaching in Luque et al. (2002) that alteration of these amino acid residues would affect the inhibition of the activity of the caspases; even if binding to apoptosis stimulators were eliminated or curtailed, there could still be anti-apoptotic activity due to the inhibition of caspases.

Under the legal standards applicable to enablement, such as those of the holding of In re Marzocchi, it is not reasonable to use information from a system that may be unrelated or distantly related to argue that enablement is not present. On that reasoning, no biotechnology patent claim would survive an assertion of lack of enablement. Enablement only requires a likelihood of reproducibility by one of ordinary skill in the art, not a guarantee of absolute reproducibility.

The same standards are applicable to the teachings of D. Vucic et al., "A Mutational Analysis of the Baculovirus Inhibitor of Apoptosis Op-IAP," J. Biol. Chem. 273: 33915-33921 (1998) ("Vucic et al. (1998)"). Even though it may be true that most of the conserved amino acid residues were essential to the protein's ability to inhibit apoptosis, and

though it may be true that most of these conserved residues were not required for binding to Hid, the apoptosis stimulator, this still does not give rise to a *prima facie* case of lack of enablement. The same is true of the finding that a region at the carboxy-terminal end of BIR2 was essential for binding to Hid and that binding to Hid was necessary but not sufficient to block Hid-induced apoptosis. These results may possibly lead to the conclusion that even though it is possible to determine which amino acid residues in a protein molecule are conserved in different family members, it is not possible to predict which of these conserved residues are critical to the various different functions of a multifunctional protein. That conclusion, however, still does not lead one of ordinary skill in the art to the conclusion that there is a significant likelihood that the claims as amended lack enablement. It is not necessary to modify all of these residues, or even a significant portion of them. It is not fatal to enablement that some inoperative embodiments are within the scope of the claims. As above, these teachings do not address the issue that the proteins encoded by the claimed nucleic acid segments can inhibit apoptosis by regulating the activity of at least one caspase.

Similarly, I. Takada et al., "Alteration of a Single Amino Acid in Peroxisome Proliferator-Activated Receptor-α (PPARα) Generates a PPARδ Phenotype," Mol. Biotechnol. 14: 733-740 (2000) ("Takada et al. (2000)"), cannot create a *prima facie* case of lack of enablement. The teachings of Takada et al. (2000) are directed to an entirely different class of protein than the proteins encoded by the nucleic acids of the present invention. There is no relationship shown between peroxisome proliferators-activated receptors (PPARs) and the anti-apoptotic proteins encoded by the nucleic acids of the present invention. At best, the teachings of Takada et al. (2000) raise the possibility that certain amino acid changes could alter the activity of the proteins encoded by the nucleic acid sequences of the present invention. However, in the absence of any relationship between the amino acid changes reported in Takada et al. (2000) and any features of the secondary or tertiary structure of the proteins encoded by the nucleic acid sequences of the present invention, such a possibility remains pure speculation. Under the holding of Marzocchi, such speculation should not be used to create a *prima facie* case of lack of enablement.

The same reasoning applies to the teachings of H. Guo et al., "Protein Tolerance to Random Amino Acid Change," Proc. Natl. Acad. Sci. U.S.A. 101: 9205-9210

(2004) ("Guo et al. (2004)"). Firstly, the amino acid changes in Guo et al. (2004) were not conservative; they were in fact random. The PCR mutagenesis technique used in Guo et al. (2004) did not yield conservative amino acid substitutions; some of the mutations were indels or frameshifts. Despite this, only 34% on average of the random mutations in the sequence of a protein were predicted to create a disruption in secondary or tertiary structure that was great enough to cause the inactivation of a protein. It is logical that this percentage would be considerably lower if the mutations had been limited to those that introduced conservative amino acid substitutions.

At page 14 of the Office Action, it was stated that claims 2-6 were directed to a genus of nucleic acids that encode a polypeptide that is capable of inhibiting apoptosis in insect cells, mammalian cells, or plant cells, or a polypeptide that is capable of inhibiting caspase-9, including nucleic acid molecules encoding a polypeptide comprising SEQ ID NO: 2. However, it was stated in Q. Huang et al., "Cloning and Characterization of an Inhibitor of Apoptosis Protein (IAP) from *Bombyx mori*," Biochim. Biophys. Acta 1499: 201-208 (2001) ("Huang et al. (2001)"), that, while the peptide of SEQ ID NO: 2 was capable of inhibiting apoptosis in *Spodoptera frugiperda* Sf-21 insect cells induced by p35-deficient *Autographa californica* nucleopolyhedrovirus (AcMNPV) and of inhibiting apoptosis in mammalian cells induced by Bax, it was not capable of inhibiting apoptosis in mammalian cells induced by Fas. The specification makes similar assertions at page 34, lines 3-5.

The Office Action, therefore, goes on to reach the conclusion that the various different members of the family of IAPs, which are the counterparts of BmlAP in other organism, are not functionally equivalent to BmlAP or SflAP. While this conclusion may be true, it has no bearing on whether or not the requirements for enablement under the first paragraph of 35 U.S.C. § 112 are satisfied. The claims do not require inhibition of Fas-induced apoptosis in mammalian cells. All that is required is that subject matter within the scope of the claims be reasonably enabled by the specification. See In re Hogan, 194 U.S.P.Q. 527, 537 (C.C.P.A. 1977) (scope of enablement must be commensurate within the scope of the claims). It is not proper to unduly burden Applicants by requiring enablement for features or limitations that are not actually recited in the claims.

The same conclusion is reached from the assertion that Huang et al. (2001) states that BmlAP and SfiAP did not inhibit caspase-3 or caspase-7. The claims do not

require the inhibition of caspase-3 or caspase-7. Similarly, the assertion that the protein *Autographa californica* IAP is ineffective in inhibiting apoptosis in both mammalian and insect cells does not lead to a conclusion of lack of enablement. There is no reason to conclude, from this teaching, that the proteins encoded by nucleic acids according to the present invention, would not inhibit apoptosis.

Similar reasoning leads to the conclusion that the teachings of R. Takahashi et al., "A single BIR Domain of XIAP Sufficient for Inhibiting Caspases," J. Biol. Chem. 7787-7790 (1998) ("Takahashi et al. (1998)"), do not give rise to a *prima facie* case of lack of enablement. In fact, Takahashi et al. (1998) teaches that a single BIR domain is sufficient to inhibit caspase-3. There is no basis to conclude from this result that the claims encompass inoperative subject matter. The claims do not specify any degree of inhibition of apoptosis and do not require that all routes of apoptosis are inhibited.

The teachings of M.C. Abraham & S. Shaham, "Death Without Caspases, Caspases Without Death, Trends Cell Biol. 14: 184-193 (2004) ("Abraham & Shaham (2004)"), also do not give rise to a *prima facie* case of lack of enablement. The fact that cell death can occur through processes other than those mediated by the activity of caspases does not lead one of ordinary skill in the art to reach the conclusion that the claims are not enabled for the inhibition of apoptosis that is mediated by routes other than caspases. There is no requirement that the claims be enabled for the inhibition of apoptosis or other cell death processes that are not mediated by caspases.

With respect to the comments at page 17 of the Office Action, there is no evidence of record that suggests that the polypeptide of SEQ ID NO: 2 would not be effective in inhibiting apoptosis in insects other than lepidopteran insects. The assertion that "insects are highly divergent" does not constitute evidence that leads to the conclusion that the polypeptide of SEQ ID NO: 2 cannot inhibit apoptosis in non-lepidopteran insects.

With respect to activity in plant cells, the articles of L.-H. Yu et al., "Induction of Mammalian Cell Death by a Plant Bax Inhibitor," FEBS Lett. 512: 308-312 (2002) ("Yu et al. (2002)") and H. Kuriyama & H. Fukuda, "Developmental Programmed Cell Death in Plants," Curr. Opin. Plant Biol. 5: 568-573 (2002) ("Kuriyama & Fukuda (2002)"), do not give rise to a *prima facie* case of lack of enablement, even for plant cells. The fact that a specific orthologue of mammalian Bax-1, namely *Arabidopsis thaliana* AtBI-

1, does not inhibit apoptosis in mammalian cells, but appears to stimulate it, does not prove the converse; i.e., that a protein that inhibits mammalian apoptosis would not necessarily inhibit it in plants (even *Arabidopsis*). Similarly, the difference between apoptosis in metazoans and in plants, as set forth in Kuriyama & Fukuda (2002) does not suggest that there is a lack of enablement for these claims.

With respect to claims 13, 14, 17, and 19, directed to transformed host cells that can be used to generate transgenic animals or plants, the arguments put forth in the Office Action at pages 19-20 also do not create a *prima facie* case of enablement. This is true notwithstanding the teachings of L.M. Houdebine, "Production of Pharmaceutical Proteins from Transgenic Animals," J. Biotechnol. 34: 269-287 (1994) ("Houdebine (1994)"), M.A. Ayliffe et al., "Aberrant mRNA Processing of the Maize *Rp1-D* Rust Resistance Gene in Wheat and Barley," Mol. Plant-Microbe Interactions 17: 853-864 (2004) ("Ayliffe et al. (2004)"), and P.R. Day, "Genetic Modification of Plants: Significant Issues and Hurdles to Success," Am. J. Clin. Nutr. 63: 651S-656S (1996) ("Day (1996)"), and F. Cellini et al., "Unintended Effects and Their Detection in Genetically Modified Crops," Food Chem. Toxicol. 1089-1125 (2004).

This is true for the following reasons. Firstly, the claims to transformed cells have other utilities than for the production of transgenic organisms. One of ordinary skill in the art can use such transformed cells for other purposes, such as screening assays or for the production of recombinant proteins. The utility and enablement of claims to transformed cells cannot be evaluated on the basis that their sole usefulness is in the production of transgenic organisms.

Secondly, the references cited above at most support the proposition that there is some degree of experimentation required for the use of the transformed cells in transgenic organisms, and there is some possibility that some attempts to produce transgenic organisms will be unsuccessful or will produce transgenic organisms that have properties other than the desired properties. As clearly elucidated above, this proposition is insufficient to give rise to a *prima facie* case of lack of enablement. The fact that the phenotype of the transgenic animal may not always be completely predictable or that the transgenic embryo may not always be viable does not create a *prima facie* case of enablement. As emphasized above

with respect to the facts and holding of In re Wands, a success rate of 100% in complex technologies is neither expected nor required.

With respect to the specific issues raised in regard to transgenic plants in Day (1996) and Cellini et al. (2004), the fact that the copy number may not always be precisely controlled or the site of integration of the introduced DNA may not always be known or precisely controlled, or the fact that other compounds may be produced by the transgenic plants, does not negate the existence of enablement under the first paragraph of 35 U.S.C. § 112. Again, enablement does not require that all species within a claim function equivalently or perfectly.

The foregoing issues under the enablement requirement of the first paragraph of 35 U.S.C. § 112 are resolved by considering the following principles of case law:

(1) Actual evidence of unpredictability, rather than the intrinsic nature of an art area itself, is what give rise to an enablement concern. In re Cook, 169 U.S.P.Q. 298 (C.C.P.A. 1971).

(2) One need not necessarily disclose how to make each and every embodiment encompassed by a claim, even in relatively unpredictable arts. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976).

(3) Claims are not necessarily invalid even if they encompass some inoperative embodiments. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984).

(4) The possible existence of some possibly deleterious side effects, such as the potential production of toxins by transgenic plants, does not give rise to a lack of enablement. In re Anthony, 162 U.S.P.Q. 594 (C.C.P.A. 1969) (possible side effects of drug used to treat mental depression not sufficient to allow conclusion of lack of enablement).

(5) Claims that may include considerable numbers of inoperative embodiments, but only if factors are included that would be excluded by one of ordinary skill in the art, are enabled as long as it "would be obvious to one of ordinary skill in the relevant art how to include those factors in such manner as to make the embodiment operative other than inoperative." In re Cook, 169 U.S.P.Q. 298, 302 (C.C.P.A. 1971). In other words, it is improper to add variables that would be unreasonable to one of ordinary skill in the art and would never be applied by one of ordinary skill in the art, such as extremes of temperature,

and then demand enablement in the face of those variables. Similarly, it is not the function of the claims to specifically exclude possible inoperative substances. In re Dinh-Nguyen, 181 U.S.P.Q. 46 (C.C.P.A. 1974).

(6) There is no requirement under the first paragraph of 35 U.S.C. § 112 that all of the claimed compounds must possess the same degree of utility. In re Gardner, 177 U.S.P.Q. 396 (C.C.P.A. 1973).

In addition, the claims as amended require that the polypeptide encoded by the nucleic acid segment has the property of "inhibiting the activity of a caspase." This functional language, which more clearly defines the activity of the polypeptide, must be taken into account in evaluating the enablement of the claims. In re Halleck, 164 U.S.P.Q. 647 (C.C.P.A. 1970). This is another reason why enablement exists for these claims.

Accordingly, the claims are enabled throughout their scope and the Examiner is respectfully requested to withdraw the rejections as applied to the amended claims.

IV. THE REJECTIONS OF CLAIMS 13, 15, AND 19 UNDER 35 U.S.C. § 102(b)

Claims 13, 15, and 19 were rejected under 35 U.S.C. § 102(b) as anticipated by K. Fatyol et al., "Molecular Characterization of a Stably Transformed *Bombyx mori* Cell Line: Identification of Alternative Transcriptional Initiation Sites of the A3 Cytoplasmic Actin Gene," Mol. Gen. Genet. 260: 1-8 (1998) ("Fatyol et al. (1998)) as evidenced by Q. Huang et al., "Cloning and Characterization of an Inhibitor of Apoptosis Protein (IAP) from *Bombyx mori*," Biochim. Biophys. Acta 1499: 201-208 (2001) ("Huang et al. (2001)") and the USPTO Search Reports "us-10-041-859-2.rge" and "us-10-041-859-1.rge" (collectively "the Alignments").

This rejection is respectfully traversed. The claims require a "nucleic acid sequence having at least 95% sequence identity to SEQ ID NO:1." The polynucleotide sequence listed as SEQ ID NO:1 is 3773 nucleotides in length. The fact that Fatyol et al. (1998) discloses cells producing a messenger RNA molecule that encodes a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 does not mean that there is 95% sequence identity to SEQ ID NO:1 for the corresponding nucleic acid. The amino acid sequence SEQ ID NO: 2 is 347 amino acids long, which means that the nucleotide sequence disclosed in Fatyol et al. (1998) is 1041 bases, not 3773 bases. There is absolutely no

teaching or disclosure of the remaining 2732 bases in Fatyol et al. (1998). These bases form the flanking sequences and are either 5′ or 3′ to the open reading frame (ORF) that is translated.

There is no interpretation of this data that can allow anticipation of a 3773-base nucleic acid segment by a teaching of 1041 bases. The 95% identity criterion would require 3584 bases. There are still over 2500 bases unaccounted for. The number of possible combinations of those bases is astronomical. For only 10 bases, there are 1,048,576 possible sequences of those 10 bases, and only one of them is correct if identity is to be maintained.

Even the teachings of the Alignments (page 23 of the Office Action) leads to the conclusion that there are approximately 1056 bases unaccounted for, or approximately 868 bases if the 95% identity criterion is taken into account. The number of possible sequences of 868 bases is 4^{868}, or a number greater than 10^{99}. This means that there can be no teaching of the identical sequence, or even a 95% identical sequence, because there is no way to determine or predict the sequence of the large number of missing bases. The probability of obtaining the correct sequence by chance is exactly the same as the probability of flipping a fair coin 1736 times and having it come up heads each time. Even if one flipped the coin only 100 times, there still would be approximately 1.26×10^{30} sequences of results.

A rejection under 35 U.S.C. §102 requires that the claimed subject matter be described in its entirety in a single reference. Kalman v. Kimberly-Clark Corp., 218 U.S.P.Q. 781, 789 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984). In re Marshall, 198 U.S.P.Q. 344 (C.C.P.A. 1978). Missing elements cannot be supplied by the knowledge of one skilled in the art or by the disclosure of another reference. Structural Rubber Products Co. v. Park Rubber Co., 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984).

The absence of at least 868 bases, in the interpretation that leaves the smallest number of bases unaccounted for, absolutely precludes any finding of anticipation. The invention, which is a sequence of 3773 bases, cannot be considered to be described "in its entirety" by a reference that fails to disclose at least 868 bases of the claimed sequence. There is no "broadest reasonable interpretation" of the claims that can remove 868 bases from a 3773-base sequence. It does not matter whether the sequence is considered as DNA or RNA; there is simply no disclosure of a significant portion of the sequence.

The sequence of the missing 868 bases cannot be considered inherent in the teachings of Fatyol et al. (1998). Inherency "may not be established by probabilities or possibilities." Continental Can Co. USA v. Monsanto Co., 20 U.S.P.Q. 2d 1746, `749 (quoting In re Oelrich, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). As shown above, the probability of obtaining the correct nucleotide sequence for the missing 868 bases is vanishingly small. This precludes anticipation under the theory of inherency.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

V. CONCLUSION

In conclusion, the claims remaining for consideration particularly point out and distinctly claim that which Applicants regard as their invention. These claims meet the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112. They are free of the prior art, whether considered individually or in combination. Accordingly, allowance of these claims is respectfully requested.

If any issues remain, the Examiner is respectfully requested to telephone the undersigned at (858) 450-0099 x302.

Respectfully submitted,

Date: June 23, 2005

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